

***Cutibacterium acnes* Dysbiosis: Alternative Therapeutics for Clinical Application**

Sara Sá ^{1,2,3}, Ruben Fernandes ^{1,2,4}, Álvaro Gestoso ^{1,2}, José Mário Macedo ^{1,2,5}, Daniela Martins-Mendes ^{1,2,4}, Ana Cláudia Pereira ^{1,2,4,*} and Pilar Baylina ^{1,2,6,*}

¹ FP-BHS—Biomedical and Health Sciences Research Unit, FP-I3ID—Instituto de Investigação, Inovação e Desenvolvimento, FFP—Fundação Fernando Pessoa, 4249-004 Porto, Portugal; saravs@ufp.edu.pt (S.S.); ruben.fernandes@ufp.edu.pt (R.F.); agestoso@ufp.edu.pt (Á.G.); coelhomacedo@gmail.com (J.M.M.); danielamm@ufp.edu.pt (D.M.-M.)

² HE-FP—Hospital Fernando Pessoa, CECLIN—Center of Clinical Studies, 4420-096 Gondomar, Portugal

³ FMUP—Faculty of Medicine, University of Porto, 4420-319 Porto, Portugal

⁴ FCS—Faculty of Health Sciences, Fernando Pessoa University, 4220-150 Porto, Portugal

⁵ Faculty of Biology, Department of Functional Biology and Health Sciences, University of Vigo, 36310 Vigo, Spain

⁶ ESS—School of Health, IPP—Polytechnic Institute of Porto, 4200-072 Porto, Portugal

* Correspondence: anacpereira@ufp.edu.pt (A.C.P.); pilarbaylina@ess.ipp.pt (P.B.)

Table S1. Brief description of the clinical trials, over the last decade, for *Cutibacterium acnes* infection in acne vulgaris (AV) treatment.

Author	Aim	Subjects	Methodology	Outcomes
2022 Hsieh-Hsun Ho, et al. [30]	Perceive the effect of fermented postbiotics on the skin health.	20 volunteers (8 males and 12 females). The average of age was 28 years old. 11 volunteers had oily skin and 8 had severe AV.	The formulation was incorporated into a cosmetic gel and applied on volunteers twice a day at a dosage of 3 to 5 mg/cm ² for 4 weeks. Every subject received on the right and left sides of the face the "A" gel (TAC/collagen gel) and a "B" gel (placebo lotion). Two different types of face gels and specific parameters were evaluated on each patient: the skin's moisture score, the sebum content, inflammation, the AV symptoms, porphyrins, and brown spots improvement.	The formulation significantly reduced the redness and the inflammation in the treatment group. In the TAC/collagen gel-treated group, the acne lesions significantly improved after only one week and were healed by week 2 in the treatment group. The formulation also promotes the reduction of the porphyrin number accumulation and skin brown spots.
2022 Hye Sung Han, et al. [31]	Measure the effect of the <i>E. faecalis</i> CBT SL-5 extract could be utilized for normalizing skin microbiota and clinically improve AV.	20 healthy Korean volunteers (11 men and 9 women) diagnosed with mild (65%) to moderate (35%) AV. The patients age range was between 19 and 38 years (26.5 ± 5.9).	The treatment was composed of the vehicle lotion (control) and the vehicle lotion with the <i>E. faecalis</i> CBT SL-5 extract (isolated from a healthy Korean human fecal sample). The patients were instructed to apply approximately 0.5–1 g of either test or vehicle lotion to the corresponding side of their face twice daily for 4 weeks.	The improvements in the patients with mild acne were faster than the patients with moderate acne. The phylogenetic diversity of the skin swab samples from the test side significantly decreased when compared to the initial state. In contrast, at the control side, no significant decrease was observed at 2 and 4 weeks after treatment. Overall, the test lotion was well tolerated, with similar safety profile to that of the vehicle lotion.
2021 Sunatra Nitayavardhana, et al. [40]	Compare the efficacy and the safety of once and alternating twice-weekly light-emitting diode (LED) treatments in moderate to severe acne.	Thirty healthy subjects with skin phototypes III (3/30, 10%), IV (22/30, 73.3%), and V (5/30, 16.7%) with moderate to severe AV as defined by Burton's grading score.	The first group was treated with a standard regimen by weekly irradiating with the blue LED light for 15 minutes and the red LED light for another 15 minutes at 3 days apart for a total of four blue and four red LED irradiation sessions in 4 weeks. The second group was treated once a week with the blue and red light consecutively on the same day, for 15 minutes, each for a total of four blue and four red LED irradiation sessions in 4 weeks.	Mild erythema lasting 30 to 60 minutes was observed at the end of the treatment in all patients of both groups. In the one-week treatment, there was a statistically significant reduction in the number of inflammatory acne ($P < 0.001$) from baseline until the final follow-up visit. In the alternating twice-weekly group, there were no side effects reported in the study.
2021 Wan-Hua Tsai, et al. [32]	To perceive the effects in the <i>Lactobacillus plantarum</i> -GMNL6 on the maintenance of healthy skin.	15 females; age ranged between 25 and 50 years old.	The treatment was made on the right side of the face. The participants used base cream including heat-killed <i>L. plantarum</i> -GMNL6 and on the left face of the participants' face, they used only the base cream.	The amount of <i>C. acnes</i> significantly decreased in the <i>L. plantarum</i> -GMNL6 treatment. The patients showed a decrease in the red areas and porphyrins with the treatment with heat-killed <i>L. plantarum</i> -GMNL6.
2020 Shilpi Jain, et al. [41].	Evaluate the clinical pharmacokinetics and safety of single and of multiple doses of VB-1953 on	12 patients (33,3% males and 66,7% females) aged 18–45 years with moderate to severe facial AV. The	All subjects applied VB 1953 (2%) gel on the entire face twice daily (every 12 h) from Day 1 morning until Day 15 morning. Pharmacokinetic assessment was evaluated by sequential blood	There was a reduction in the inflammatory lesions of 59,77% on the 15 th day when compared to the lesions observed at the baseline. Additionally, on Day 15 there was a reduction of around 13,05% in the

	adult subjects with facial AV.	subjects had at least 20 inflammatory lesions (papules, pustules, and nodules/cysts) on the face.	collection and safety was measured by assessments of local skin reactions.	noninflammatory lesions in the patients when compared to the baseline.	
2019	Natcha Chotta wornsa k, et al. [42]	Test the efficacy and the safety of Ketoconazole (KTZ) cream in adult female affected by AV.	41 females with age between 25 and 49 years old were divided into two groups: 20 females in the KTZ 2% cream group and 21 females in the placebo cream group. The mean age of each group was 35,2 and 34,1 years, respectively.	The participants were instructed to apply the cream on their entire face twice daily for 8 weeks. At the end of week 8, the females discontinued using the cream and were evaluated for another 2 weeks (a 10-week study period in total) to evaluate the lasting KTZ effect. The outcome assessments were measured at baseline.	The proportion of participants with AV improvement from baseline (42.9% vs. 9.5%, P = 0.015) and the success rate (45.0% vs. 14.3%, P = 0.043) were significantly higher in the KTZ group when compared to the placebo group. The common side-effects found in the KTZ group were itching (25%) and dryness (15%), which spontaneously resolved without discontinuation of the treatment or additional medications.
2019	Ante Karogla n, et al. [33]	Gather further evidence on the feasibility, safety, and efficacy of direct microbiome modulation by transferring beneficial <i>C. acnes</i> strains in patients with acne-prone skin.	14 patients (men and women), with age 18–23 years old and mild to moderate AV.	The study comprised 2 phases: an active induction phase with 5% benzoyl peroxide gel (BPO, 7 days) and an interventional microbiome treatment phase (5 weeks). In the first phase, BPO was used for significant depletion of the skin microflora. After clearing the ecological niche, the new <i>C. acnes</i> strains were applied in phase 2 to colonize the skin.	The transplantation of the beneficial strains of <i>C. acnes</i> did not lead to deterioration of the acne lesions but clinical improvements were observed in comedone (noninflamed lesions) counts when comparing end-of-treatment with the baseline assessments in both treatment groups. Although no significant improvement was observed in inflamed lesions (papules and pustules) compared to the baseline, there were no reported adverse events.
2019	Nirmanika Wishwa kala Nawara thne, et al. [43]	Develop topical cosmeceutical formulations incorporating <i>N. sativa</i> and evaluate the antibacterial activity of those formulations against selected bacteria as alternative antiacne agents at a commercial scale.	50 patients with AV.	The agar well diffusion method was the method employed to determine the antibacterial effect of the gel formulations against <i>S. aureus</i> and <i>C. acnes</i> (under anaerobic condition). The acute local irritation of the optimized gel formulation was tested in 50 subjects with AV, was applied on the right ear lobe of each individual, and signs of hypersensitivity reactions (pruritus, oedema, and erythema) were observed after 30 min.	Among the three solvents tested, the formulation F3 displayed the highest activity against both bacterial species, <i>S. aureus</i> and <i>C. acnes</i> . Out of the 50 participants, only 7 (14%) developed some signs of hypersensitivity.
2019	Natalja Weber, et al. [44]	Evaluate the degreasing effect and skin tolerability of a botanical face cleanser with hops and willow bark extract and disodium cocoval	21 healthy volunteers (15 women and 6 men) aged between 21 and 49 years (average age 29 ± 7 years).	The volunteers washed their faces over the course of 17 days under specific variated instructions using a standard product containing sodium laureth sulfate as positive control. The sebum level of the skin surface was determined using a Sebumeter®. Skin erythema was quantified using a Mexameter®.	After 15 days of treatment, the SLES showed a statistically significant degreasing effect. However, after the application break of 48 hours, the sebum reduction was no longer statistically significant. The botanical face cleanser showed a statistically significant reduction in the sebum content only on day 17

		glutamate when compared to a standard face cleanser with sodium laureth sulfate (SLES).			after the application break. None of the face cleansers caused skin redness during the study.
2019	Joon Hyuk Hou, et al. [45]	Identify and compare the active antimicrobial ingredients in red ginseng with other benzoyl peroxide and azelaic acid in the treatment of <i>C. acnes</i> .	31 female volunteers and 20 men and woman aged 19 to 40 years old affected by mild to moderate acne symptoms and without severe or chronic physical illnesses.	The patch-tests soaked with antimicrobial ingredients were applied to the upper backs for 24 hours and readings were performed on Days 0, 1, and 2. At Weeks 0, 2, and 4, the oil contents, oxidized sebum, and redness of skin were evaluated. The number of white/blackheads, papules, and nodules on the face of the subjects were also evaluated.	The oil contents significantly decreased after 2 and 4 weeks (<0.05) after application of the cream in the patients. The oxidized sebum contents of skin also decreased after 2 and 4 weeks (<0.025), and skin redness statistically decreased four weeks (<0.05) after application. Clinical evaluation of 4 weeks showed that white/blackheads and papules decreased significantly after 2 and 4 weeks (<0.025) compared with before use.
2018	Seung-Hwan CHOI, et al. [46]	Comparison between the antimicrobial effects of indocyanine green (ICG)- and methyl aminolevulinate (MAL)-based photodynamic therapy (PDT) on <i>C. acnes</i> in an in vitro experiment and in clinical experiment with two types of PDT with different light sources and comparable ICG concentrations.	21 patients (15 males and 6 females) with acne were divided into two groups; the 830 nm LED group had a mean age of 23.92 ± 3.88 and the 805 nm diode laser of 24.25 ± 4.77 years old.	The clinical assay involved a group of 21 patients who were diagnosed with acne and received 0.2% ICG on the patients' lesions, and after 15 min, they irradiated them with an 830 nm LED or 805 nm diode laser. The lesion severity was determined using the Korean Acne Grading System (KAGS), and the number of standard lesions, nodules, and papules were counted.	In the clinical trial, the KAGS scores significantly decreased in all the patients after the treatment when compared to the pretreatment KAGS scores. The changes in KAGS scores after the two different treatments (830 nm LED and 805 nm diode laser groups) were not significantly different ($P = 0.570$).
2018	Mi-Ran Kim, et al. [47]	Analyze the satisfaction of patients with AV relative to the application of the BPO 5% gel in conjunction with the liquid cleanser and the photoprotective moisturizer (moisturizer Sun Protection Factor, SPF 30) in the treatment of AV.	50 patients (17 males and 33 females): 37 patients with mild AV and 13 with moderate AV. 21 patients were less than 18 years old, 25 were aged between 18 to 25 years old, and 4 patients were more than 35 years old.	The face was cleansed with a liquid cleanser twice daily (morning and evening), moisturized with SPF 30 once a day, and the BPO 5% gel was applied topically once a day (in the evening or in the morning after washing with the cleanser). The patients were evaluated at baseline, week 1, week 4, week 8, and week 12. The treatment was applied for 12 weeks.	Most of the participants (approximately 87%) reported being content to very satisfied, including 33% reporting being extremely satisfied, showing favorable tolerability. After 12 weeks of treatment, there was a 72% reduction in the overall number of lesions. From week 1 (89% reduction from baseline in orange fluorescence pixels), the treatment plan was successful in lowering <i>C. acnes</i> , and this result was still slightly preserved at week 12 (74% reduction).
2017	Brigitte Dreno, et al. [48]	Analyze the microbiota profile on skin areas with acne lesions (comedones as well	55 subjects with skin phototypes II (45%), III (49%), IV (4%), or VI (2%) were evaluated.	For 28 days, each patient's half-face received daily applications of a topical antibiotic. On Days 0, 14, and 28, the inflammatory and noninflammatory lesions were assessed. AV severity was	On Day 0, individuals had an average of 19 papulo-pustular lesions and 31 comedones across their entire face. On Day 28, analysis revealed that the dermocosmetic reduced both <i>Actinobacteria</i> and <i>Staphylococcus spp.</i> , while

		as papulo-pustular lesions) and of nonacne lesions visible skin. Then, in a split-face study, compare the changes in these communities using either a topical antibiotic or a dermocosmetic for 28 days.	The group's ages ranged from 15 to 43. All the subjects had mild to moderate acne vulgaris (AV) with at least 20 comedones and 10 papulo-pustular lesions evenly spaced throughout the face.	scored using the GEA grading scale. Samples of the skin microbiota were collected from 26 subjects (11 males and 15 females). Using molecular biology methods, the microbiota were detected.	erythromycin reduced the quantity of <i>Actinobacteria</i> . After 28 days, there was no discernible difference between the tested products in the number of inflammatory and noninflammatory lesions ($P > 0.05$). The patients tolerated both products well.
2017	Makoto Kawashima, et al. [49]	Evaluate the safety and the efficacy of long-term BPO in an open label, randomized, multicenter study by the administration of 2.5% or 5% BPO gel once daily for 52 weeks to patients who suffer from AV.	458 patients (144 males and 314 females) suffering from AV. Patients were aged between 12 and 49 years old. Only 393 patients completed the study.	The patients were divided in half and randomized to receive BPO 2.5% gel ($n = 198$) or BPO 5% gel ($n = 195$). The patients applied the gel once a night every day for 52 weeks. The acne lesions were counted on the first day (baseline) and on weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Bacteriological evaluation was performed at the beginning and at the end of the study. The treatment safety was evaluated through skin tolerability scores and laboratory tests such as hematology, blood chemistry, and urine analysis.	The number of total lesions (TLs) suffered reductions in both treatment groups. The median TL had reductions over the weeks in both groups, and at week 52, the percentage reduction was of 75.3% in the 2.5% BPO group and 80.4% in the 5% BPO group. The adverse effects with possible relation to the treatment were mild in severity and were 49.4% (114/231) for 2.5% BPO group and 55.1% (125/227) for 5% BPO.
2016	Ying Ma, et al. [43]	Compare the antimicrobial activities of a triple antibiotic ointment (TAO), a fusidic acid (FA) cream, and a mupirocin ointment against strains of <i>C. acnes</i> isolated from patients admitted to a hospital of Shanghai, China.	98 patients (36 females and 62 males). The age of the patients varied from 14 to 36 years old. All the patients included suffered from facial acne.	The strains of <i>P. acnes</i> were collected to a brucella-supplemented medium and were identified through an API-20A system. The MICs to the antibiotics (mupirocin, fusidic acid, clindamycin, erythromycin, neomycin sulfate, bacitracin, polymyxin and TAO) was tested in the isolates in vitro in the brucella agar.	The isolated <i>C. acnes</i> strains were 49.3% resistant for erythromycin, 33.4% for clindamycin, and 27.5% exhibited cross-resistance to erythromycin and clindamycin. The susceptibility to the tested antibiotics was significantly higher in the isolates recovered from patients with mild to moderate acne than the ones recovered from patients with severe AV.
2016	C. Richter, et al. [50]	Perceive if the UVA photographic techniques among them the Visiopor® PP 34 can provide an accurate determination of the fluorescence quantity and if it can objectively classify the acne severity in patients.	24 Caucasian and nonsmoking patients (9 male and 15 female), aged between 18 and 25 years old. All patients suffered from mild to severe AV (Investigator Static Global Assessment, ISGA score 2 and 4). Body mass index	Patients were randomized to receive the treatments in a split-face design for 25 days. 12 of the 24 patients received tyrothricin 0.1% on one side of the face and BPO 5% on the other side. The remaining 12 patients received tyrothricin 0.1% on one side of the face and a combination of clindamycin and BPO on the remaining side.	Results showed that there was a stronger association between fluorescence quantity and inflammatory lesions than with noninflammatory lesions. In skin face areas with lower amount of <i>C. acnes</i> , there was an inferior correlation to the fluorescent levels detected such as the jawbone. All the treatments achieved a reduction in the total ISGA score and individually in the inflammatory and noninflammatory lesions observed. The sebum levels increased in all the areas of the skin tested (forehead, cheek, chin, and jawbone).

			(BMI) mean of 22.5.	
2016	Ying Ma, <i>et al.</i> [51]	Perceive the impact of the use of photodynamic treatment (PDT) in the long-term management of AV through the immunological behaviors in keratinocytes.	52 patients (35 males and 17 females) with nodulocystic AV, classified in the type IV of the Pillsbury classification, aged between 16 and 27 years old.	<p>The patients applied a 5% 5-aminolevulinic acid (ALA) powder to the lesions on the surface of skin and covered it with plastic wrapping. After 2 hours, the patients washed their faces. Then each patient received 3 sessions of a whole-face irradiation from an LED device. These irradiations were pursued in an interval of 7–10 days. From the other side were collected punch biopsies from peri-lesional acne areas on 8 patients before and after the ALA-PDT treatment and from two other normal tissues (controls) from patients who underwent facial surgery.</p> <p>In the clinical trials the effectiveness of the treatments of ALA plus PDT increased throughout the time of the study. Briefly, the total effective rate in first follow-up, at the 2nd week, reached 92.31%, and on the last, 8th, week, it reached 96.12%. The viability of the keratinocytes decreased gradually with the increase of the radiation and the apoptosis was more obvious in the blue-light than in the red-light group.</p>
2016	Nayera Hassan Mofteh, <i>et al.</i> [52]	Study the efficacy of PDT using intense pulsed light (IPL) and liposomal methylene blue (LMB) versus the use of IPL alone in the improvement of the acne vulgaris lesions on the patient's back.	35 subjects (21 males and 14 females). The age mean was 23.7 ± 4.7 years old. All the patients had acne lesions, 22 on the face and in the back and 13 patients only on the back.	<p>The patients washed their back with soap and water, then the area was cleaned with isopropyl alcohol. Then one half side of each patient's back received a topical liposomal methylene blue hydrogel and the side was covered with a silver reflective plastic wrap for 60 min (PDT-treated side). Then both sides were irradiated by a single pass of IPL with a 550 nm cut-off filter. This treatment was repeated once a week for 3 weeks. Lesions were counted according to the Burton's acne severity scale.</p> <p>At baseline there was no significant difference between the lesion counts on each back side of the patients. In all of the patients, a significant reduction ($P < 0.005$) was observed in the number of total, inflammatory, and noninflammatory lesions. A comparison of both sides revealed that the PDT side showed better improvement in both inflammatory lesions and total lesions ($P < 0.005$), although there was not a significant improvement in the noninflammatory lesions ($P = 0.231$) when compared with the improvement on the IPL side.</p>
2015	Porntip Pan-In, <i>et al.</i> [53]	Use of manufactured cellulose-based nanoparticles with alfa-mangostin (anti-acne compound) in the treatment of AV.	20 human volunteers. Age 15–24 years old (16 females and 4 males) nonpregnant, and not-breastfeeding subjects.	<p>Skin irritation of the particles was evaluated in 20 human volunteers using single application closed patch test (on the upper back of the subjects for 24 hours) and repeated application open patch test (on the subject's arm, twice a day, for 14 days). AV therapeutic effect of the mangostin nanoparticles was preliminarily evaluated in 10 AV patients (3 males and 7 females) for a month.</p> <p>After the 4 weeks post first application, the side applied with 1.2% mangostin nanoparticle gel (treated side) showed a significantly larger decrease in both the ASI value ($P = 0.042$) and the inflammatory lesion ($P = 0.035$) than the side applied with gel base (control side).</p>
2015	Michele Pezza, <i>et al.</i> [54]	Determine the effects of the administration of inositol in the treatment of polycystic ovary syndrome (PCOS) patients affected by AV.	100 female patients affected by acne and PCOS.	<p>Group A (n = 50) received 2 g of inositol, via oral intake, twice a day for 6 months. Group B was administered 200 micrograms of a placebo also 2 times a day, for 6 months. The patients were followed-up for 3 months after the end of the treatment.</p> <p>Group A patients showed an extensive improvement of the skin in the clinical evaluations, fewer papulopustular lesions, and no evident inflammation. In group B, 40 patients exhibited no improvement, except for 2 patients who showed a minor clinical improvement. DHEAS blood concentration decreased in group A and remained essentially unaltered in group B.</p>

2013	Sang Mi Han, et al. [55]	Verify the bee venom antibacterial effect and assess the effectiveness of cosmetics containing purified bee venom (PBV) in the management of acne vulgaris.	12 males with mild to moderate acne, as graded by KAGS. Age between 12 and 35 years of age.	The subjects were randomly assigned in a 1:1 ratio to receive a total of 4 mL of either cosmetic containing PBV (containing 0.06 mg/mL of bee venom, n = 6) or cosmetics without PBV (n = 6) to the entire face, twice daily in the morning and evening for two weeks. The number of inflammatory and noninflammatory lesions served as an indicator of efficacy.	The patients that received the treatment of PBV showed a significant success ($P = 0.001$) when compared to the control group. Additionally, the treatment group showed, in the 2-week treatment period, a significant decrease in the <i>C. acnes</i> counts ($P = 0.012$).
2013	Takigawa a M, et al [56].	Evaluate and compare the efficacy and safety of a formulation with adapalene and nadifloxacin to a formulation with moderate adapalene alone.	185 Japanese patients (60 males and 125 females). Age between 12 and 53 years old. 74 patients suffered from moderate AV and 14 from severe AV.	The inflammatory acne lesions were treated with adapalene 0.1% (n = 101) or the combination of adapalene and nadifloxacin 1% (n = 87), gel once a day at night for 12 weeks. Patient's inflammatory lesion (pustules and papules) were counted by the investigators every 2 weeks till the end of the treatment.	At week 4, combination therapy significantly reduced symptoms (45%) compared to monotherapy (24%). Combination therapy was more effective than monotherapy at both 8 and 12 weeks (combination therapy, 66%; monotherapy, 51%; $P = 0.0056$ vs. monotherapy).

Table S2. Brief description of the clinical trials, over the last decade, for *Cutibacterium acnes* infection in post-surgery shoulder infections.

Year	Author	Aim	Subjects	Treatments	Outcomes
2022	Symonds T, et al. [57]	Reduce superficial and deep colonization of <i>C. acnes</i> in patients undergoing a preoperative skin preparation for total shoulder arthroplasty (TSA).	105 patients undergoing a TSA with age equal to or higher than 18 years old.	Group 1 received a standard pHisoHex wash (1% triclosan; sodium benzoate, 5 mg/mL; and benzyl alcohol, 5 mg/mL), group 2 received benzoyl peroxide (BPO) (5%), and group 3 received BPO (5%) with clindamycin (BPO-C) (1%).	All 3 topical skin preparations demonstrated a reduction in the <i>C. acnes</i> colonization. The application of pHisoHex reduced the skin colonization by 50%, BPO reduced the skin colonization by 73.7%, and the BPO-C reduced skin colonization by 81.5% ($P = 0.003$).
2022	Ines Unterfrauner, et al. [58]	Investigate the efficacy of a topical AV cream, benzoyl peroxide miconazole nitrate (BPOMN), to reduce subcutaneous and capsular <i>C. acnes</i> in individuals undergoing open shoulder surgery.	120 adult patients (54 males and 66 females). Mean age 59 years old. 60% of the patients had positive <i>C. acnes</i> cultures.	The adults were divided into two groups (1:1): a 7-day preoperative application of BPOMN on the preoperative skin (intervention group) or no cream (control group) from 1 November 2018 to 31 May 2020. The treatment was applied once a day during the 7 evenings preceding the elective surgical procedure.	The topical 7-day preoperative skin application of acne cream significantly reduced the intraoperative <i>C. acnes</i> load in 56% of the patients in the intervention group compared with 16% of the control patients.

2021	Eric J. Cotter, <i>et al.</i> [59]	Compare the efficacy of blue light therapy (BLT) and 5% topical BPO gel in combination with a chlorhexidine (CHX) preparation in eradicating <i>C. acnes</i> at the deltopectoral interval.	60 volunteers (healthy male individuals). Age equal to or greater than 18 years old.	The participants were divided into 3 groups of treatments: BPO, BLT, or both BPO and BLT. The group of BPO applied 5% gel to the axilla, anterior shoulder, and lateral shoulder after showering in the morning and evening, for 3 days. BPO and BLT groups shoulders were treated with 2% CHX gluconate solution with 70% isopropyl alcohol.	There was no significant difference in the side effects of the participants in each group. BPO-BLT had the better reduction in <i>C. acnes</i> concentration, followed by the BPO group ($P < 0.05$ for each). BLT alone did not demonstrate effective antimicrobial properties against <i>C. acnes</i> . The addition of CHX to BPO further enhanced the effects, as demonstrated by the 0.03 odds of growth in the treatment arm.
2021	Gagan Grewal, <i>et al.</i> [60]	Study the effect of the dermal application of 3% hydrogen peroxide (HP) in the reduction of the rate of positive <i>C. acnes</i> cultures collected intraoperatively.	60 patients (29 males and 31 females) under undergoing primary shoulder arthroplasty.	All patients were treated with a standard surgical skin preparation. Electrocautery was used to incise through the dermal layer. Following electrocautery opening of the dermal layer, patients in the hydrogen peroxide group ($n = 30$) received application of 3% sterile-filtered HP along the entire dermis using a soaked surgical sponge.	There was no significant difference in the incidence of positive cultures between the HP and control group (20% vs. 16%, $P > 0.99$). Subgroup analysis by gender and age demonstrated that the males aged 69 years or younger had a higher incidence (44%) of positive cultures than older men (23%) and older women (4.4%).
2021	Beat Kaspar Moor, <i>et al.</i> [61]	The efficacy of an additional decontamination of the subcutaneous layer in the <i>C. acnes</i> culture rate in primary open shoulder surgery.	108 patients undergoing open shoulder surgical procedures.	After the incision of the skin and one subcutaneous layer of tissue, the intervention (disinfection) group (70 patients) received an additional preparation with povidone-iodine (PVP-I) solution.	A significantly higher proportion of <i>C. acnes</i> positive samples were found in male patients, although no correlation was found between BMI and the contamination of the operating field. In primary open shoulder surgery, the disinfection of the subcutaneous tissue decreased, by 2, the positive culture rate of the operating field for all germs combined ($P = 0.036$) and even more for <i>C. acnes</i> ($P = 0.013$).
2021	Vendela M. Scheer, <i>et al.</i> [62]	Test the effects of the topically applied BPO to decrease the skin load of <i>C. acnes</i> in treatment of AV in patients subjected to elective shoulder surgery at different stages of the procedure.	100 patients (63 males and 37 females) scheduled for elective shoulder surgery. Age range between 20 and 82 years old.	The treatment group (55 subjects) received, in the morning and evening of the 2 days prior to surgery, a 5 cm strip of 5% BPO gel to the shoulder. The last 2 applications were made after showering and on the morning of the day of surgery. The control group (45 subjects) only applied the soap.	Men had a fivefold higher amount of <i>C. acnes</i> on untreated skin. Treatment with BPO considerably lowered <i>C. acnes</i> both before and after skin disinfection compared to the control group ($p = 0.001$). This positive effect of BPO persisted until skin closure, the point at which some recolonization of <i>C. acnes</i> had occurred, but to a higher degree in the control group ($p = 0.040$).
2021	Dorothea Dörfel, <i>et al.</i> [63]	Test the effects of two antiseptics, the 2% w/v chlorhexidine gluconate (CHG) with 55% w/v isopropanol (IPA)	16 Caucasian healthy volunteers (7 males and 9 female). Age range	Each patient received a total of 4 treatments: two different antiseptics (CHG-ALC or PVP-I-ALC) and 2 different contact times per antiseptic (2.5 min or 30 min). The treatments were applied on Day 1 and on Day 4 in	<i>C. acnes</i> was the most predominant bacteria on the anaerobic plates. The treatment PVP-I in combination with alcohol (3.24% w/v with = 76% w/v alcohol) had a small superiority when compared to the 2% w/v CHG with 55% w/v IPA. I-ALC applied for 30 min was

		preparation and a PVP-I and alcohol preparation (3.24% w/v PVP-I, 38.9% w/v IPA, 37.3% w/v ethanol) on the shoulder region of healthy volunteers.	between 22 and 74 years.	both shoulders and samples were collected at time 0 h and 3 hours after the application.	significantly more effective than CHG-ALC applied for 2.5 min ($p < 0.01$), but not more effective than CHG-ALC when applied for 30 min ($p = 0.06$).
2020	Jason E. Hsu, <i>et al.</i> [64]	Compare the effectiveness of home chlorhexidine washes with BPO soap in patients undergoing shoulder arthroplasty surgery to reduce <i>C. acnes</i> levels on the skin surface and incised wound edge.	49 male patients planning to undergo shoulder arthroplasty.	The first group received a bottle of 4% CHG group ($n = 25$). The second group received a bar of 10% BPO group ($n = 24$). Both groups were instructed to apply the wash or soap to the surgical shoulder the night prior to and the morning of surgery and to scrub for at least 60 seconds with the wash.	All the swabs collected from the skin were shown to be positive and of similar load for <i>C. acnes</i> in the two groups (CHG 1.6 ± 1.1 vs. BPO 1.5 ± 1.4 , $p = 0.681$). The percentages of dermal cultures that were positive were not significantly different between the two groups (CHG 61% vs. BPO 46%, $p = 0.369$). The <i>C. acnes</i> load on the incised dermal edge was also similar between the two groups (CHG 0.8 ± 1.0 vs. BPO 0.8 ± 1.4 , $p = 0.991$).
2020	Floor M. van Diek, <i>et al.</i> [65]	To evaluate the effect of BPO application on the presence of <i>C. acnes</i> in the shoulder of healthy human volunteers.	30 (11 males and 19 females) healthy volunteers aged 40 to 80 years with positive culture results for <i>C. acnes</i> on the skin of the right shoulder.	The participants were divided in half and the treatment group received BPO Teva hydrogel, 50 mg/g, 5%, and the placebo group a Carboneerwatergel 1% FNA 100 g, hydrogel. Both groups applied the gel for 2.5 days: 3 times in the morning and 2 times in the evening.	The treatment group had a <i>C. acnes</i> reduction on the shoulder of 51.4% after application of BPO when compared with placebo application. Nine participants experienced side effects. The side effects included itching, redness of the skin, and a warm feeling on the skin where the gel was applied.
2020	Justin D. Stull, <i>et al.</i> [66]	Evaluate the efficacy of HP as an addition to standard sterile preparation for shoulder surgery.	140 male patients undergoing shoulder arthroscopy.	Both control group ($n = 70$) and the study group ($n = 70$) received a standard preoperative sterile preparation; the treatment group received an additional HP to preoperative preparation (five 3% HP-soaked gauzes).	17.1% patients in the HP group and 34.2% patients in the traditional group had positive cultures for <i>C. acnes</i> ($P = 0.033$).
2019	Peter N. Chalmers, <i>et al.</i> [67]	Determine whether preoperative skin preparation with HP can reduce intraoperative <i>C. acnes</i> culture positivity.	65 patients undergoing shoulder arthroscopy.	In the peroxide group ($n = 30$), the skin was whipped with 3% HP between the alcohol and Chloraprep steps. Then both groups followed the same standard operation methodology.	Only in males were the results in the 3 positive cultures significant. Fewer patients within the peroxide group had 3 positive cultures (0% vs. 31%, $P = 0.048$) and in the glenohumeral joint (8% vs. 44%, $P = 0.044$) when compared to the control group.

2018	Douglas S. Hancock, <i>et al.</i> [68]	Compare a single application of BPO combined with 2% CHX/alcohol as a skin preparation prior to shoulder surgery to 2% CHX/alcohol in the <i>C. acnes</i> inhibition.	22 male participants undergoing shoulder arthroscopy. Mean of age 30 years old.	Each patient's shoulder was randomized to receive the treatment of 5% BPO wash plus 2% CHX/alcohol or the control applications (two applications of 2% chlorhexidine/alcohol).	The application of topical BPO cream in addition to chlorhexidine/alcohol at the time of surgery did not provide a superior inhibition of <i>C. acnes</i> when compared to the two applications of chlorhexidine/alcohol.
2018	Mitchell L. Smith, <i>et al.</i> [69]	Demonstrate a lower prevalence of <i>C. acnes</i> with the use of a wound protector drape during shoulder surgery.	47 patients (22 males and 25 females) undergoing shoulder surgery. Median age of 70 years old.	After dissecting through the delto-pectoral interval, the wound protector drape was inserted, with the deep ring placed under the deltoid laterally, and deep in the pectoralis major tendon medially, to isolate the superficial tissues. Once the prosthesis was implanted, the surgical procedure was carried out.	The Incidence of <i>C. acnes</i> on the barrier drape 2/47 patients was less when compared to the subdermal layer. <i>C. acnes</i> incidence was 10/47 patients at the end of the operation, risk ratio 0.2 (95% confidence interval 0.06–0.70), $P = 0.008$. This study did not use a control group.
2018	Davide Blonna, <i>et al.</i> [70]	Comparison between a single skin preparation (PVP-I) and a double skin preparation (CHG followed by PVP-I) as a preoperative skin preparation to prevent postoperative infections.	40 patients (8 males and 32 females) undergoing shoulder surgery. Age range between 45 and 88 years old.	The single skin preparation consisted of the use of sterile gauzes soaked with 1% PVP-I (10% of iodine available) and 50% isopropyl alcohol. For the double skin preparation, the skin was first washed with a soap solution of 4% chlorhexidine gluconate. Then they applied 10% PVP-I and 50% isopropyl alcohol as described in the single skin preparation.	Coagulase-negative staphylococci (CoNS) dropped from 92.5% to 40% and to 7.5% after the single and double skin preparation ($p < 0.001$), respectively. The positivity rate was reduced from 50% to 17.5% ($p = 0.002$) and from 27.5% to 0% ($p = 0.001$) for <i>C. acnes</i> and <i>S. aureus</i> , respectively, with no difference between the two preparations.
2018	Logan Kolakowski, <i>et al.</i> [71]	The comparison of BPO compared with CHG on the <i>C. acnes</i> skin burden in patients undergoing shoulder surgery	80 patients (49 males and 44 females) undergoing shoulder surgery. Age range between 18 and 88 years old.	Patients were randomized to 5% BPO gel or 4% CHG skin cleanser. Each group of patients applied the solution over the operative shoulder and axilla for 3 mornings before surgery. Patients left the applied solution for three minutes then washed it every morning.	A statistically significant decrease in positive cultures for <i>C. acnes</i> was observed in the BPO-treated side compared with the control shoulder ($P = 0.0003$). No change in positive cultures for <i>C. acnes</i> was observed for the CHG-treated side when compared with the control shoulder ($P = 0.80$).
2018	Thilo Patzer, <i>et al.</i> [72]	Compare the positive <i>C. acnes</i> in the glenohumeral and in the subacromial space in primary shoulder arthroscopies with	115 patients (63 men and 52 females) undergoing shoulder surgery. Age range between 18	Direct harvesting of a soft tissue biopsy specimen was performed during arthroscopy after standard skin disinfection, starting either in the subacromial region or the glenohumeral space, according to a prospective randomization scheme.	36.5% of the skin swabs, collected after surgical disinfection, were positive for <i>C. acnes</i> . The <i>C. acnes</i> positive results in the superficial samples were 28.2% for the anterolateral approach, 14.9% for the deltopectoral approach, and 36.6% and 17.0% in the deep tissue samples, respectively. 11 patients of the 42 patients

		an intact rotator cuff.	and 76 years old.		with positive skin swab culture results presented matching positive results for <i>C. acnes</i> in the biopsy specimen.
2018	Kotaro Yamakado [73]	Examine the contamination rate of <i>C. acnes</i> and other bacteria in the anchor sutures of 2 different surgical skin preparation solutions with or without a plastic adhesive drape in the arthroscopic rotator cuff repair procedure.	126 patients (88 males and 38 females) who underwent arthroscopic rotator cuff repair.	The 126 patients were divided into four groups: PVP-I (n = 31), PVP-I with plastic drape (n = 33), CHX-alcohol (n = 30), and CHX-alcohol with plastic drape (n = 32), related to the treatment applied. Then one of each group received an additional adhesive plastic drape with antibacterial nonimpregnated barriers.	<i>C. acnes</i> positive cultures were identified in 47% of the PVP-I group, 33% in PVP-I with a drape, 33% of the CHX-alcohol group, and 9.3% of the CHX-alcohol with a drape group. <i>Staphylococcus</i> isolates were identified in 3% of the PVP-I with drape group and 6% of the CHX-alcohol with drape group. No infections occurred in any of the patients for the 12-month follow-up.
2017	Hailey H. Dizay, et al. [74]	Investigate the possibility of reducing the incidence of <i>C. acnes</i> in the shoulder joint with the application of a topical gel with a combination of BPO 5% and C phosphate 1.2%.	65 patients (43 males and 22 female) undergoing shoulder surgery. The patients age range was between 28 and 79 years old.	Patients applied BPO/C to the operative shoulder once a day before the day of surgery, at night. The patients were evaluated for signs of infection on the 10th and 21st day and monthly for 6 months after surgery. Patients with positive deep <i>C. acnes</i> cultures were administered with oral doxycycline 100 mg daily for 3 weeks.	31 of the 65 patients had <i>C. acnes</i> -positive swabs prior to receiving topical BPO/C therapy. Male patients were colonized more frequently than female patients ($P = 0.001$). By the day of surgery, the treatment had removed 74.2% of <i>C. acnes</i> skin colonization. Deep <i>C. acnes</i> contamination of the shoulder joint at the surgery site dropped from 19.6% to 3.1% ($p = 0.006$).
2017	Lisa Johansson, et al. [75]	Comparison of the infection rate in patients undergoing a shoulder replacement between the use of Eclipse® prosthesis and other types of shoulder replacements.	241 patients (109 males and 132 females) undergoing shoulder replacement.	102 patients received the Eclipse® prosthesis (65 males and 27 females), whereas the remaining patients received one of five different other implants (Bigliani®, CTA, Delta®, Epoca, and Univers™).	There was a statistically significant difference ($p = 0.002$) in the infection-free survival after 4 years between the Eclipse® group (88.8%; CI 82.5–95.7) and the control group (95.7%; CI 87.7–100.0).
2015	Geoffrey S. Marecek, et al. [76]	Study the effect of axillary hair removal on the reduction in the bacterial burden in the shoulder surgery.	85 males undergoing shoulder surgery. Age range between 21 and 53 years old.	The hair of one axilla in each patient was removed with a surgical clipper. Then both shoulders were prepared with 2% chlorhexidine gluconate and 70% isopropyl alcohol for the surgical procedure.	CoNS was the most often isolated organism prior to surgery in 72.9% of cases, followed by <i>C. acnes</i> in 72.4% of cases and <i>Corynebacterium</i> species in 17.1% of cases. Following the surgical preparation, <i>C. acnes</i> 4.1%, CoNS 3.5%, and <i>Bacillus</i> species 1.2% were identified. Age or the amount of axillary hair had no effect on the overall bacterial load in each axilla.

Table S3. Brief description of the clinical trials, over the last decade, for *Cutibacterium acnes* infection in other iatrogenic infections.

Year	Author	Aim	Subjects	Treatments	Outcomes
2018	Anna Gomes, <i>et al.</i> [77]	Comparison between the use of sonication and the standard microbiological workup in the recovery and identification of pathogens in patients with infective endocarditis.	61 heart valves obtained from 55 subjects that underwent heart valve replacement for noninfection-related to hemodynamic failure or presumed infective endocarditis.	For this study, a standard microbiological workup (with or without molecular testing) and two different sonication protocols (broth enrichment vs. centrifugation) of heart valves were compared.	The addition of sonication/centrifugation significantly increased the yield of microbiological testing from 6/26 to 17/26 ($p = 0.003$). Additionally, the addition of both sonication/centrifugation and 16S-PCR increased the yield of microbiological testing even more, from 6/26 to 22/26. Sonication/enrichment yielded many false positive results in negative controls (28.6%; 10/35), mainly <i>C. acnes</i> contaminations. <i>C. acnes</i> was the most isolated contaminant in negative control valves (total 7/35).
2018	M. M. Ploeger, <i>et al.</i> [78]	Identify contaminations in the ready-to-use surgical draping kits or in surgeon gloves in patients undergoing primary total hip arthroplasty (THA).	43 patients (19 males and 24 females) with THA. Age range between 19 to 82 years old. The mean of preoperative of C-reactive protein (CRP) was $5.7 \text{ mg/l} \pm 6.1$ and the leukocyte count was $7.9 \text{ G/l} \pm 2.6$.	Samples were removed during the THA surgery. The first was when the joint capsule was incised too deep, and the second was at the end of surgery, before wound closure. The third sample was 10 milliliters (ml) of liquid aspirated with a sterile 10 mL syringe and transferred into sterile containers.	Bacterial detection showed no correlation to either preoperative leukocyte or preoperative serum CRP level. But the detection showed a correlation to the duration of surgery, when longer than 90 min, and the increase in the positivity of collected samples.
2018	Ivany Machado de Carvalho Baptista, <i>et al.</i> [79]	Identify the microbial diversity present in the oral cavity and in the bronchoalveolar lavage (BAL), endotracheal aspirate, intensive care unit (ICU) patients on invasive mechanical ventilation (IMV) at different periods of	10 patients (6 males and 4 females) with age between 35 and 85 years old. Poor oral hygiene was observed in all the patients, and 9 patients had supragingival calculus. These patients were submitted to an OTI or to IMV.	Initial samples were taken 12 hours after orotracheal intubation from bronchoalveolar lavage, two locations in the mouth: gingival sulcus, collected with paper cone, and dorsal side of the tongue, collected with swab. Using a 12 siliconized polyvinyl chloride (PVC) tracheal aspiration probe, samples were taken from the endotracheal aspirate, gingival sulcus, and dorsal side of the tongue after 48 and 96 hours.	The results indicate the possibility of bacterial species migration from the mouth and upper airways during orotracheal intubation.

		oro-tracheal intubation (OTI).			
2016	Ste'phane Litrico, <i>et al.</i> [80]	Investigate the clinical outcomes of using standard reusable instrumentation in patients undergoing instrumented posterior lumbar fusion employing single-use surgical instruments, with particular attention to the surgical site infection.	Test group consisted of 49 patients (21 male and 28 female) with degenerative disc disease, canal stenosis, or degenerative spondylolisthesis. The group where reusable instrumentation (previous group) was employed consisted of 100 patients (41 men and 59 female).	All patients underwent posterior lumbar interbody fusion or transforaminal lumbar interbody fusion. The patients were followed up for a minimum of 1 year to perceive any possible symptoms of infection and to check their Oswestry Disability Index (ODI).	The pre- and postoperative ODI of the test group was lower ($p < 0,001$) than the ODI in the previous group ($p < 0,001$). Additionally, the test group only had 1 case of deep infection by <i>Staphylococcus aureus</i> (2% of the patient group); on the contrary, the previous group using reusable instruments had 6 cases of deep infection (6% of the patient group), 3 cases of <i>Staphylococcus aureus</i> , and 3 cases of <i>C. acnes</i> .
2013	K. Falk-Brynhildsen, <i>et al.</i> [81]	Perceive the effect of the use of plastic adhesives in the bacterial recolonization of the skin and surgical wound contamination of patients undergoing cardiac surgery.	135 patients (109 males and 26 females) undergoing cardiac surgery.	The patients were divided into two groups; one was draped with adhesive plastic drapes (n = 68), the other without (n = 67, control group). Bacterial samples were taken preoperatively before disinfection with chlorhexidine in ethanol and immediately after disinfection. Intraoperative samples were collected every hour of the surgery from both the exposed and the adjacent subcutaneous wound tissue skin.	At the end of the surgery, they observed a significantly higher CoNS positive result in subcutaneous tissues of the group treated with adhesive drape, of 14.7%, when compared to the control group, 4.5% ($p = 0.044$).
2013	U. M. Rieger, <i>et al.</i> [82]	Investigate the role of bacterial biofilm in the pathogenesis of capsular contracture through an optimized sonication protocol in the bacterial identification of removed breast implants.	121 breast implants from 84 patients (2 males undergoing gender reassignment and 82 women) were collected and analyzed in this study. The patients ages ranged between 19 and 80 years old.	10 sterilized breast implants were included in the study as negative controls. During the surgery, the surgeons assessed the breast firmness using the Baker manual scale. The microbiologic evaluation included the use of the sonification (with a BactoSonic® ultrasound bath).	The positive sonication cultures correlated with the degree of capsular contracture ($p < 0.001$). Implants with 3 months of implantation that needed surgical revision had a statistically higher rate of positive sonication cultures than non-needed revision implants ($p = 0.043$). The negative breast implants controls remained negative in the protocol applied.

Table S4. Brief description of the clinical trials, over the last decade, for *Cutibacterium acnes* infection in other skin pathologies.

Year	Author	Aim	Subjects	Treatments	Outcomes
2020	Jennifer P. Craig, <i>et al.</i> [83]	Evaluate the efficacy of Manuka honey, complexed with a-cyclodextrin, in a microemulsion (MHME) eye cream application in patients with blepharitis.	53 participants (32 females, 21 males) with clinical signs of blepharitis	Participants were randomly assigned to apply the MHME eye cream to either the left or right eye once a day, at night, for a period of 90 days. Each day, a strip of the product was applied to the treated eye, over the periocular skin of the closed upper and lower eyelid. Clinical measurements were performed at baseline, day 30, and day 90 of the treatment period.	During the 3-month treatment period, ocular Demodex, <i>Corynebacterium macginleyi</i> , and <i>C. acnes</i> load decreased significantly in treated eyes (all $p = 0.001$). Only 5 participants (9%) reported transient ocular stinging and discomfort following accidental application of product close to the eyelash margin or due to the use of an excessive amount of eye cream.
2021	Rituja Saxena, <i>et al.</i> [84]	Study the impact of coconut oil application on the scalp microbiome (bacterial and fungal) of individuals with healthy scalps and dandruff.	140 Indian women, 70 with healthy scalps, and 70 with dandruff. The women's age range was between 20 and 45 years old.	32 subjects with dandruff scalp and 33 with healthy scalp received controlled oil treatment twice a week for 12 weeks. The treatment consisted of 20 min of scalp massage with 10 ml of pure coconut oil followed by two hours leave-on, and then a bland shampoo wash (20 mL). The remaining 33 subjects with dandruff scalp and 33 with healthy scalp were subjected to only the shampoo wash twice a week for 12 weeks.	The analysis showed a significantly lower alpha-diversity of the fungal population ($p \leq 0.001$) in the healthy scalp baseline (HB) when compared to the dandruff scalp baseline (DB). The alpha-diversity of the fungal microbiome increased significantly ($p \leq 0.0001$) after healthy scalp oil treatment (HOT) and after-shampoo application (HST) in the healthy scalp. After the treatment phase, there was a significant increase ($p = 0.01$) in the bacterial diversity in the healthy scalp after oil treatment and not with shampoo application (HST) compared to baseline.

Table S5. Brief description of the clinical trials, over the last decade, for *Cutibacterium acnes* infection in microbiome studies.

Year	Author	Aim	Subjects	Treatments	Outcomes
2013	Vijay R. Ramakrishnan, <i>et al.</i> [85]	To determine the baseline level of richness and variety in the middle meatus microbiome and to search for patterns or differences between	28 patients (18 male, 10 female) undergoing sinonasal surgery (19 septoplasty for nasal obstruction, 9 underwent endoscopic	The analysis was performed by duplex quantitative PCR assay with oligonucleotide primers for total bacteria (16S rRNA gene, FAM reporter). Pyrosequencing analysis was also performed with amplicons of the V1V3 variable region of the bacterial 16S rRNA gene (~500 bp; primers 27FYM+3 and 515R).	In all the patients, they detected the phyla <i>Firmicutes</i> , <i>Proteobacteria</i> , and <i>Actinobacteria</i> . The phylum <i>Bacteroidetes</i> was present in most subjects (83%). At the species level, <i>Staphylococcus epidermidis</i> was the most prevalent, at 96.4%, followed by <i>Staphylococcus aureus</i> , at 67.9%, and <i>C. acnes</i> , at 92.9%. These species also exhibited in the middle meatus the

healthy control patients.	approach for skull base or orbital lesions). Age range between 18 and 66 years old.	higher relative abundances (11.0%, 8.3%, and 14.7%, respectively).
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